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by

LINDA A. CORLETO

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

SYNTHETIC STUDIES OF ZIERONE

submitted by LINDA A. CORLETO in partial fulfillment of the requirements for the degree of Master of Science.

TO MY PARENTS

ABSTRACT

The hydroazulenic ring system of zierone (1) was efficiently synthesized in three steps. Photocycloaddition of 2-cyclopenten-1-one to 1-acetoxy-2-carbomethoxycyclopentene followed by thioketalization of the resulting photoadducts gave rise to a mixture of diastereomers 31a and 31b. The mixture when treated with sodium methoxide in methanol afforded keto ester 38 possessing the parent ring skeleton of 1 as well as appropriate functionalities for further modifications.

The conversion of the ketone carbonyl of 38 to the methyl group present in zierone (1) at C-10 was also accomplished. Two different routes were investigated and a total of four diastereomeric ketones 40 was obtained. Wittig reaction of 38 with methylenetriphenylphosphorane resulted in the formation of two olefins 39a and 39b. Subsequent catalytic hydrogenation of 39a and 39b gave rise to 40a and a mixture of 40b and 40c respectively. Alternatively, treatment of 38 with methoxymethylenetriphenylphosphorane followed by the acid hydrolysis of the resulting enol ethers 41 gave two diastereomeric aldehydes 42 which on Clemmensen reduction afforded 40d.

Further efforts are being made to convert the existing functional groups of 40 into the dienone system

of zierone (1). Preliminary studies showed that 40 reacted with methyllithium to give ketone 49. Treatment of the latter compound with mercuric chloride and mercuric oxide resulted in the formation of dione 50.

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INTRODUCTION

Zierone (1)*, a hydroazulenic sesquiterpene ketone was first isolated by Penfold[1] in 1926 from the essential oil of *Zieria macrophylla* (Bonpland). Preliminary studies on its structure were carried out by Bradfield, Penfold and Simonsen[2] who showed its molecular composition of $C_{15}H_{22}O$, isomeric with eremophilone.[3]

Some two decades later, Birch and his collaborators[4] renewed the investigation on the structure of this ketone and concluded that zierone is a bicyclic sesquiterpenoid possessing two double bonds, one of which, on the basis of its uv spectrum, is conjugated with a ketone carbonyl. When zierone was subjected to lithium aluminum hydride reduction and dehydration followed by the dehydrogenation of the resulting hydrocarbon, it gave a new violet azulene, zierazulene of $C_{15}H_{18}$.[4] Similarly, by reduction and dehydrogenation of its hydroxymethylene derivative, $C_{16}H_{22}O_2$, a new tetraalkylazulene, $C_{16}H_{20}$ was obtained. These two azulenes were identified[4] and confirmed[5] by unequivocal syntheses to be 2,4-dimethyl-8-isopropylazulene (2) and 2,4,6-trimethyl-8-isopropylazulene (3)** respectively.

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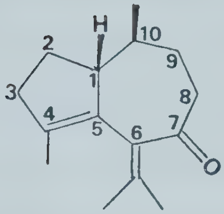
* The ring system is numbered according to the convention of hydroazulenes.

** The conventional numbering system for azulenes as indicated in structure 2 is used.

On the basis of these experimental results and spectral evidences, in conjunction with the isoprene rule, Birch and his coworkers[4] suggested provisional structure 4 for zierone.

Hildebrand and Sutherland[6] later confirmed the presence of an α,β-unsaturated ketone chromophore but found that ozonolysis of zierone gave rise to acetone as one of the fragments. These results required the presence of $(CH_3)_2C{=}\overset{|}{C}{-}\overset{|}{C}{=}O$ grouping in zierone. Accordingly, its previously assigned structure was modified to 5 or 6. These investigators also established the identity of zierone and elleryone.[6] The latter was isolated by Jones and Wright[7] in 1946 from *Evodia elleryana* (F. Muell).

Recently, Barton and Gupta[8,9] showed that none of the above structures were assigned correctly. They eliminated the possibilities of the presence of either a C-2 or a C-3 double bond on the grounds that the nmr spectrum of zierone showed the complete absence of any vinyl protons. They also conclusively showed that zierone contains the cross-conjugated dienone system $-C(Me){=}\overset{|}{C}{-}C({=}CMe_2){-}CO{-}$. The nmr studies coupled with additional chemical evidences, most convincingly, the findings that dihydrozierol 7 on ozonolysis afforded a diketone 8, allowed them to further conclude the structure 1 for zierone.



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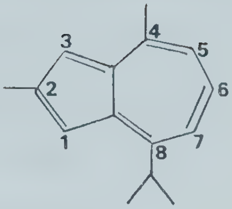

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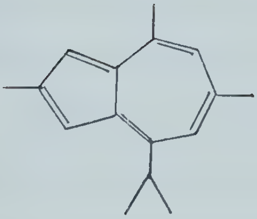

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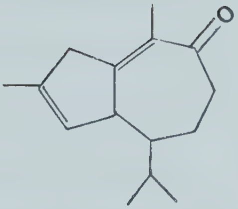

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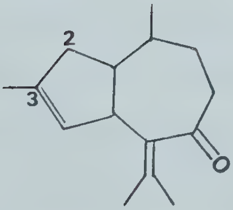

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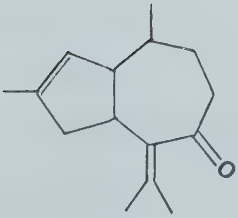

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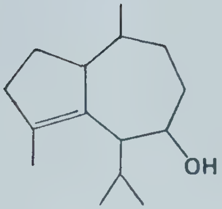
The stereochemistry of zierone remained unsettled until recently when Itô, et al.[10,11] converted gurjunene (9), a tricyclic sesquiterpene, to 10-epizierone (10). The transformation involves initially the photooxidation of gurjunene (9) and borohydride reduction of the resulting hydroperoxide to yield 11. Treatment of 11 with oxalic acid in acetic anhydride-acetic acid followed by lithium aluminum hydride reduction of the resultant acetate gave alcohol 12 which was oxidized with Collins reagent to give the C-10 epimer of zierone.

The nonidentity of zierone (1) and the partially synthetic product 10 was established spectroscopically suggesting the stereoisomeric relationship of these two compounds. Since the absolute stereochemistry of gurjunene (9) has been defined unambiguously[12], it follows that zierone has its C-10 methyl *cis* to the C-1 hydrogen atom. Furthermore, since the signs of their CD curves were found to be the same, it was concluded that they are epimeric at C-10.

Among the hydroazulenic sesquiterpenoids, the most commonly occurring ones belong to the guaiazulene (13) family of which guaiol (14) is a representative member. From the biogenetic point of view, these naturally occurring compounds are considered to possess the "normal" skeleton. A group of closely related compounds known as pseudoguaiazulenic sesquiterpenoids



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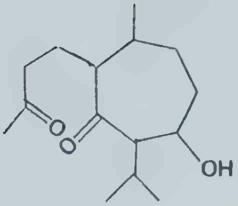

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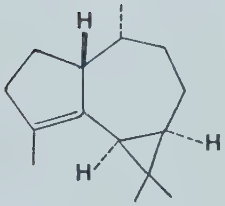

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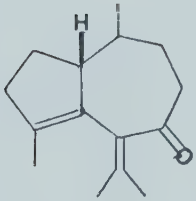

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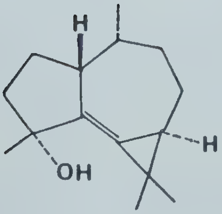

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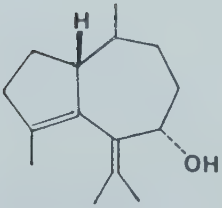

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have gross carbon skeletons as shown in tenulin (15).[13,14,15] The biogenetic formation of these compounds is believed to involve a 1,2-shift of the appropriate methyl group from a precursor of the guaiazulene type. Zierone is the only member of the so-called "Zierazulene" family. It also possesses a perturbed guaiazulene skeleton. Biogenetically, zierone could be derived from the normal guaiazulene skeleton either involving a 1,2-shift of an isopropyl group (or its equivalent)[9] or *via* the intermediacy of a cyclopropyl ring.* [9,11]

In view of the unique skeleton of zierone as well as its unusual cross-conjugated dienone system, it became of interest to undertake the synthetic studies of this compound. Furthermore, as the stereochemistry of zierone remained undetermined at the onset of the present work, it was hoped that an unequivocal synthesis of it and/or its epimer with stereochemical control would establish its stereochemistry and also confirm its assigned structure.

In general, two basic problems are involved in the synthesis of hydroazulenic sesquiterpenoids: (a) the construction of suitably functionalized hydroazulenic system and (b) the control of stereochemistry.

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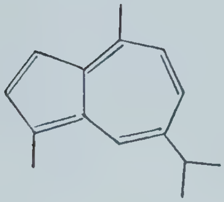
* Tricyclic guaiazulenic sesquiterpenoids possessing a cyclopropyl ring, e.g. gurjunene (9), are also naturally abundant.

Although the complexity of the stereochemistry in the present case is almost minimal, the former problem has to be solved in order to achieve an efficient synthesis of the target molecule.

During the past decade, extensive attention has been drawn towards the construction of the hydroazulene system and there have been a number of methods developed. The existing methods could be classified into the following principal categories:[16] (a) rearrangements of bicyclic compounds containing cyclohexane rings. The rearrangement of 3,3,11-trimethyltricyclo[5.4.0.$0^{2,4}$]-undeca-7,8-diol to 3,3,11-trimethyl-7-methylenetricyclo-[6.3.0.$0^{2,4}$]-undecane in the elegant synthesis of (-)-aromadendrene (16) by Büchi, *et. al.*[17] and the photochemical conversion of santonin (17) to isophotosantonic lactone (18)[18] are two representative examples. (b) Olefin cyclization. Cation-initiated olefin cyclization reactions have also found applications in hydroazulene synthesis. Some of the examples[19-26] are illustrated in Scheme I. (c) Cleavage of tricyclic compounds. Two cases[27-29] both involving the base promoted cleavage of a suitably functionalized tricyclic ring system have been demonstrated recently and are depicted in Scheme II. Since it is very much pertinent to the present work, the second device (19→20)[29] in this category is discussed in some detail as follows.



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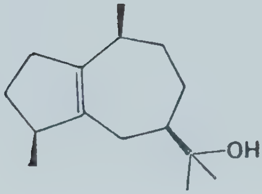

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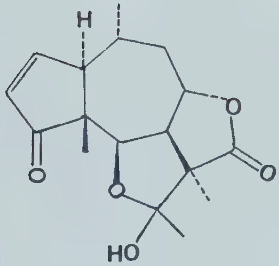

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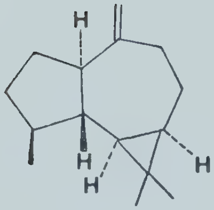

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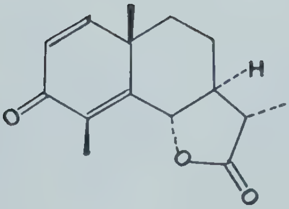

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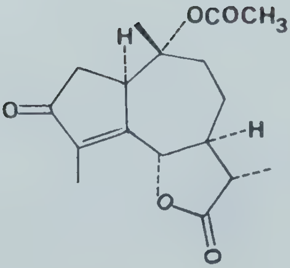

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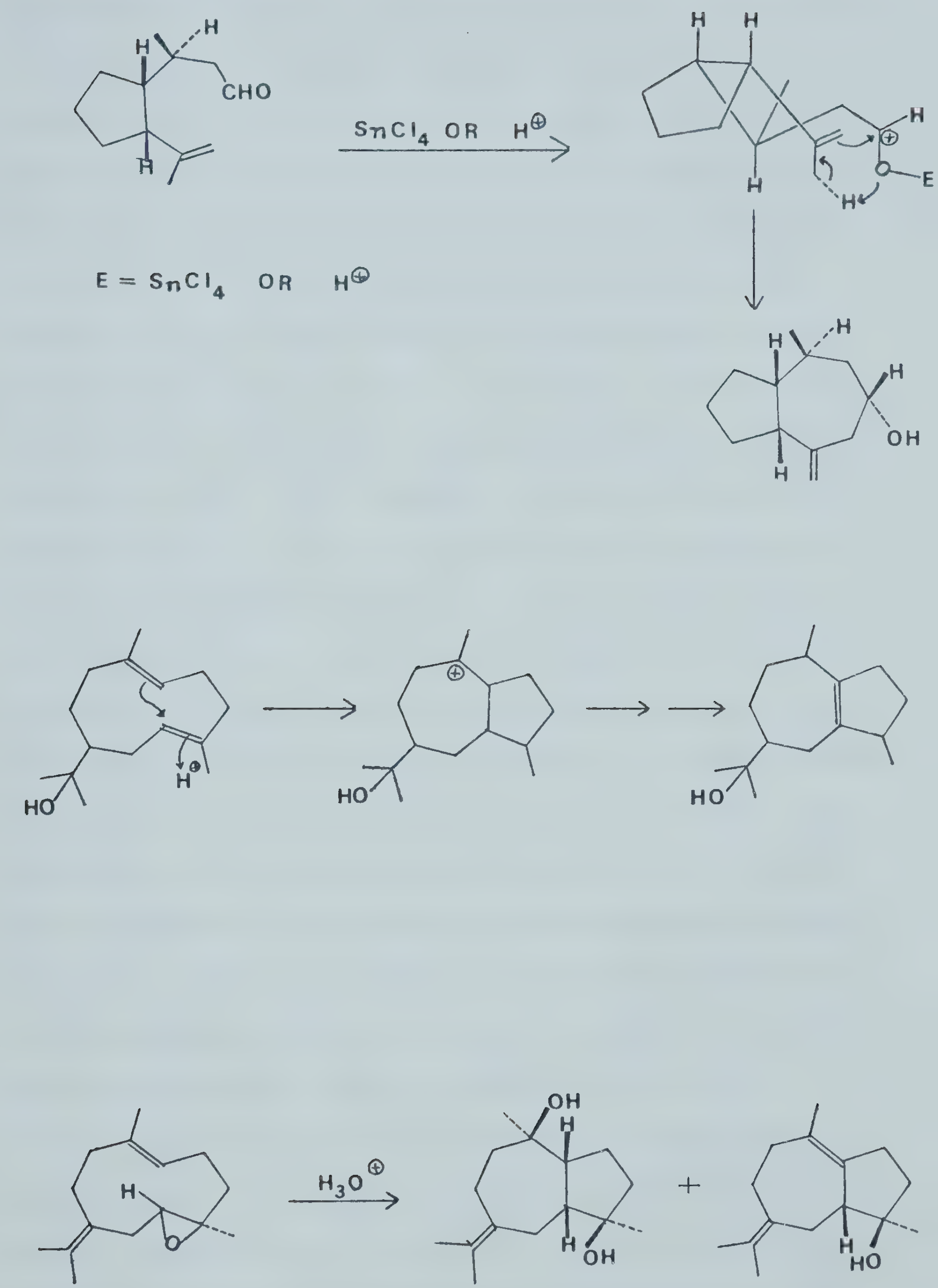
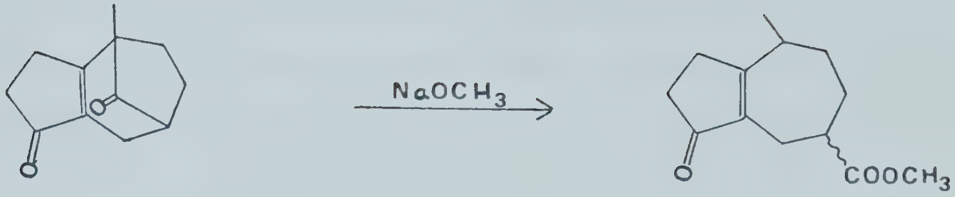
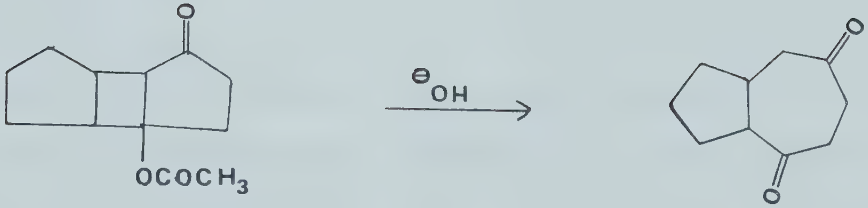
SCHEME 1


H
H
CHO
H
SnCl$_4$ OR H$^{\oplus}$
E = SnCl$_4$ OR H$^{\oplus}$
H H
H
E
H
H
H
H
OH
H
HO
HO
HO
H$_3$O$^{\oplus}$
OH
H
H
OH
H
HO
+

In principle, the hydroazulenic system can be generated by cleaving a specific bond of an appropriate tricyclic compound which embodies a bicyclo[5.3.0]-decane moiety. One of the conceivable tricycles is shown in formula 21 in which two five-membered rings are fused by a four-membered one and its modification to the type of compounds in question requires the cleavage of the highly strained four-membered ring involving bond a or b. Such an approach is facilitated by the rapid development of photocycloaddition reactions in recent years. The otherwise difficultly accessible starting material of type 21 could now be prepared in a remarkably simple fashion by photochemical fusion of two cyclopentenes. Hikino and de Mayo[29] first demonstrated the feasibility of such a scheme leading to the synthesis of a hydroazulenic compound. In their method, the required tricyclic precursor 19 was produced using cyclopentene and 3-acetoxy-2-cyclopenten-1-one as the two counterparts in the initial photochemical process. The latter compound provides adequate functionalities for the selective bond-cleavage of 19 *via* a retroaldol reaction resulting in the formation of dione 20. Clearly, such an approach is superior to the other existing ones in terms of simplicity. The particular method, however, has limited use in the synthesis of naturally occurring hydroazulenic compounds since the

SCHEME 11





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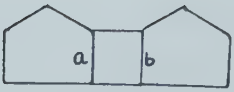

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two ketone carbonyls present would be hard to differentiate and the complete lack of functionality in the five-membered ring makes its necessary subsequent modifications difficult.* Having these in mind, a new method has been developed in this laboratory, whereby a hydroazulenic system containing adequate groupings in both rings was effectively constructed.[30] The method follows from the aforementioned principle and involves two synthetic steps. The intermediate tricyclic compound 22 was prepared with high regioselectivity by photocycloaddition of 2-cyclopenten-1-one to 1-acetoxy-2-carbomethoxycyclopentene (23). The two substituents of the latter compound were expected to reinforce the regioselectivity of the addition since they were shown to exert opposite orientational effects.[31,32] Their locations in the photoadduct 22 were further expected to facilitate the necessary bond-cleavage by a reverse Claisen-type reaction leading to hydroazulene moiety. Indeed, treatment of the photoadduct 22 by either sodium methoxide or alkali followed by esterification resulted in the formation of keto ester 24. The two ketone

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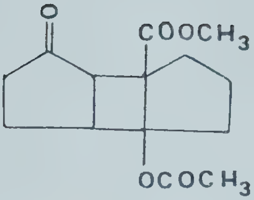
* Although, in principle, the required substituent(s) in the five-membered ring can be introduced using substituted cyclopentene as starting material in the photocycloaddition reaction, practically it is not feasible unless a symmetrically substituted one is used. The orientation of the photochemical process is expected to be difficult to control when an unsymmetrical one is involved.

carbonyls could be readily differentiated prior to the stage of the fragmentation. Thus, ketalization of 22 followed by ring fission of the resulting ketal 25 gave rise to ketal ester 26. Although the same general principle applies, the present method and that of Hikino and de Mayo[29] have practical differences. Most noticeably, in one case the cyclopentanone ring was retained and in the other it was modified to provide the seven-membered one.

The keto ester 24 and ketal ester 26 are of considerable use as synthetic intermediates for hydroazulenic sesquiterpenoids by virtue of the fact that the existing functional groups are appropriately located for further introduction of substituents and functionalities. It should be noted that, in the present case, the three carbon substituents of zierone coincide completely with the locations of the existing functional groups of keto ester 24. Hence, it is quite conceivable that the carbon skeleton of zierone could be achieved by simple direct transformations (e.g., Grignard and Wittig reactions) of these functional groups. In this connection, it was shown that its C-10 methyl could be readily introduced by a selective Grignard reaction of 26 with methyl magnesium bromide in a brief synthetic studies undertaken prior to the present work.[33] It was also found that the resulting alcohol 27 underwent



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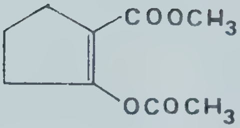

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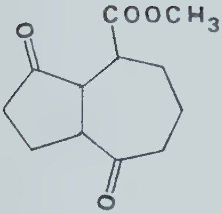

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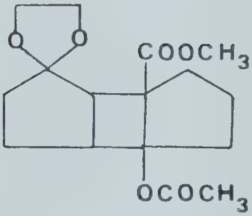

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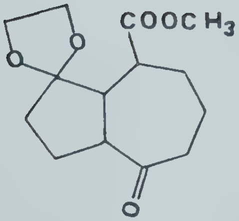

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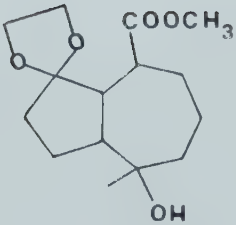

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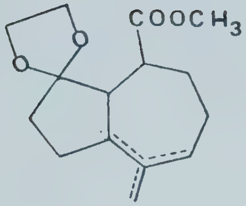
dehydration smoothly with phosphorous oxychloride in pyridine to give an isomeric mixture of 28. Attempted catalytic hydrogenation of the double bond under various conditions, however, resulted in the formation of a substantial quantity of undesirable lactone 29 suggesting that a more stable protecting group of the cyclopentanone carbonyl is necessary in order to pursue the synthesis in this direction.



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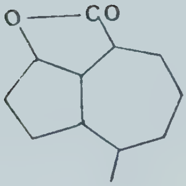

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RESULTS AND DISCUSSION

As discussed in the previous section, the locations of the three functional groups of dione 24 correspond fully to those of the carbon substituents present in zierone (1). In examining the target molecule, it is of considerable advantage to incorporate first the C-10 methyl group as the highly sensitive dienone moiety of zierone embodies the remaining carbon substituents at C-4 and C-6. Towards this end, the five-membered ketone carbonyl of 24 must be masked in advance. As discussed previously the differentiation of the two ketone carbonyls of 24 could be achieved by taking advantage of the preexisting ketone group at the initial stage of the photocycloaddition reaction. The use of dioxolane as a blocking group, however, was shown to be inadequate because it was unstable under catalytic hydrogenation conditions used in attempts to saturate the double bond of ketal ester 28. As a consequence, a less reactive protecting group was sought and thioketal was chosen for the present studies.

In order to facilitate a large scale preparation of the photoadduct 22, the previously used conditions for the photocycloaddition of 2-cyclopenten-1-one to 1-acetoxy-2-carbomethoxycyclopentene (23) were modified. Instead of isolating the product soon after the reaction was completed, additional amount of enone (in slightly

less quantity to keep the ratio of 2-cyclopenten-1-one and the olefin 23 in ca. 1:15) was introduced and irradiation was continued. This process was repeated several times before the final isolation of the photoadduct. This particular modification was time-saving in that it avoided the laborious recovery of 1-acetoxy-2-carbomethoxycyclopentene necessary for repeating the reaction in order to accumulate material in good quantity. However, the overall photochemical process for uncertain reasons appeared to be less regioselective; the photoadduct thus obtained, although homogeneous in tlc under various solvent systems contained at least two isomers as revealed by the nmr spectrum which showed two singlets each for the carbomethoxyl group (δ 3.56 and 3.53) and the acetate (δ 1.90 and 1.85). It was concluded in the later stage that the photoadduct was in fact a mixture of three isomers, 22a, 22b and 30 in approximately 2:2:1 ratio. Since efforts made to separate this mixture were fruitless, it was used directly in the following transformation.

Treatment of the mixture of photoadducts with 1,2-ethanedithiol in the presence of boron trifluoride etherate gave rise to a mixture of three isomeric thioketals in a ratio of 2:2:1 and a total yield of 68%. The minor isomer was readily isolated in the pure form by column chromatography and the others as a mixture.

Both the pure substance and the mixture showed in the spectra diagnostic ester absorption bands at 1740 cm^{-1}. In the mass spectra, molecular ion peaks were displayed at 342.0959 for the mixture and 342.0962 for the pure isomer, all in agreement with the required molecular formula of $C_{16}H_{22}O_4S_2$. The nmr spectrum of the mixture showed, in addition to the singlets at δ 3.60 ($-COOCH_3$) and 3.20 ($-SCH_2CH_2S-$), two acetate singlets at δ 2.04 and 1.98 in a ratio of 1:1 indicative of the presence of two isomers. In its nmr spectrum, the other isomer showed singlets at δ 3.64, 3.30 and 1.93 for the carbomethoxyl, thioketal and acetate protons respectively. Clearly, these spectral data revealed the isomeric nature of these compounds and this aspect was further substantiated by treating separately the mixture and the pure isomer with mercuric chloride and mercuric oxide to remove the thioketal protecting group. From the former, a mixture and from the latter, a single compound were obtained. These compounds were again shown spectroscopically (see Experimental for detail) to be isomeric and to them structures 22 or 30 could be assigned.* The structures of the thioketals could not be readily assigned on the basis of the above information as only *cis* ring juncture is stereochemically permissible in cases in

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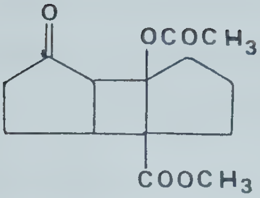
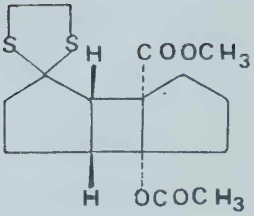
* The ring junctures are all *cis*-fused.

which a four-membered ring is fused with a five-membered one, it is certain that two of the three compounds in hand must be diastereomeric and the remaining one must possess an opposite orientation. It should be noted that the relative stereochemistry of these compounds is only of secondary concern since three of the four existing chiral centers will either be destroyed or subjected to possible epimerization in the subsequent transformations. The orientations of their functional groups are however of crucial importance for that only the compound whose acetate is oriented opposite to the ketone carbonyl is desirable for the present studies. It was necessary to ascertain their gross structures at this stage. That the mixture consists of two stereoisomers 31a and 31b with desirable orientation and the minor isomer has the opposite orientation as depicted in 32 (both ring junctures are cis and their relative stereochemistry remains to be determined) was concluded as follows.

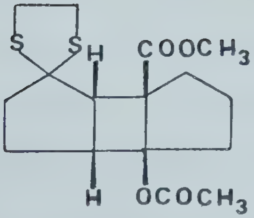
Treatment of the minor isomer with 4N sodium hydroxide in methanol gave rise to a crystalline neutral compound in 23% yield and an acidic material. The latter was subsequently esterified with methyl iodide and potassium carbonate in acetone resulting in the formation of three esters in a ratio of 2:1.5:1 and a total yield of 44% in two steps. The neutral substance


O
OCOCH$_3$
COOCH$_3$

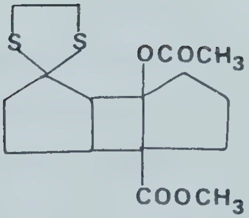
30


S
S
H
COOCH$_3$
H
OCOCH$_3$

31a


S
S
H
COOCH$_3$
H
OCOCH$_3$

31b

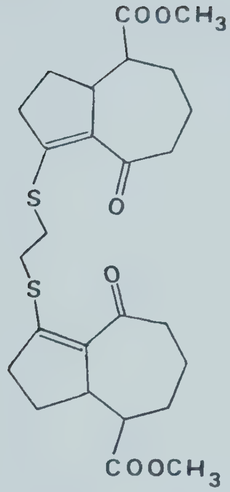

S
S
OCOCH$_3$
COOCH$_3$

32

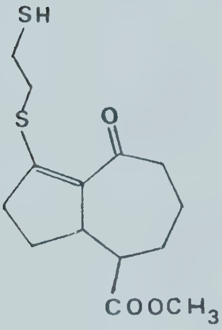
directly obtained from the hydrolysis-fragmentation reaction was shown to possess a molecular formula of $C_{26}H_{34}O_6S_2$ by its mass spectrum displaying a molecular ion peak at 506.1785. The ir spectrum showed absorption bands at 1725 and 1640 cm^{-1} characteristic of ester and conjugated enone moieties respectively. Two singlets in a ratio of 3:2 for a total of ten hydrogen atoms appeared at δ 3.7 and 3.0 in the nmr spectrum. These signals could be readily attributed to two superimposed methyl ester singlets and four equivalent protons of the two methylenes connecting the sulfur atoms. On the basis of these spectral data, its structure could be readily deduced as 33. The three esters from the acidic material were separable by column chromatography. The major product was found to be enone 34 whose ir spectrum displayed the diagnostic ester and α,β-unsaturated ketone absorption bands at 1725 and 1635 cm^{-1} respectively. The nmr spectrum showed a methyl singlet at δ 3.70 and the absence of thioketal signals normally expected at δ 3.2 region. The structural assignment was further confirmed by its mass spectrum which exhibited a molecular ion peak at 300.0863. The minor product to which structure 35 could be assigned showed an ir spectrum similar to that of 34. Both its nmr spectrum (a three-proton singlet at δ 2.17) and mass spectrum (a molecular ion peak at 314.1002) indicated however,

the presence of an additional methyl group. The ir spectrum of the remaining compound displayed two carbonyl absorption bands at 1725 (ester) and 1705 cm^{-1} (ketone) and, in its nmr spectrum, two singlets appeared at δ 3.60 (methyl ester) and 3.18 (methylenes of thioketal). On the basis of these data, structure 36 could be assigned to it. A molecular ion peak at 300 in the mass spectrum further verified the structural assignment.

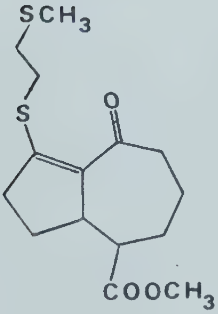
The isolation of the above compounds clearly required the precursor to possess the structural formula of 32 and its dethioketalization product structure 30. The formation of compounds 33-36 from 32 could be rationalized as depicted in Scheme III. Base hydrolysis of 32 followed by the cleavage of the cyclobutane ring *via* a reverse Claisen-type reaction gave the intermediate keto ester 36. Further hydrolysis of the ester grouping would lead to the formation of acid 36a which could further undergo β-elimination to afford enone acid 34a. Esterification of these two acids would then provide enone ester 34 and keto ester 36. The co-occurrence of enone 35 could be logically assumed as a result of partial methylation of 34. Alternatively, keto ester 36 could proceed by β-elimination directly under the influence of hydroxy ion. Two molecules of the resulting enone ester 34 could then dimerize *via*



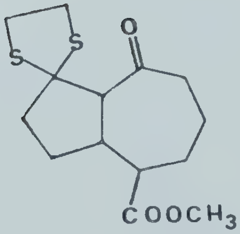
33



34

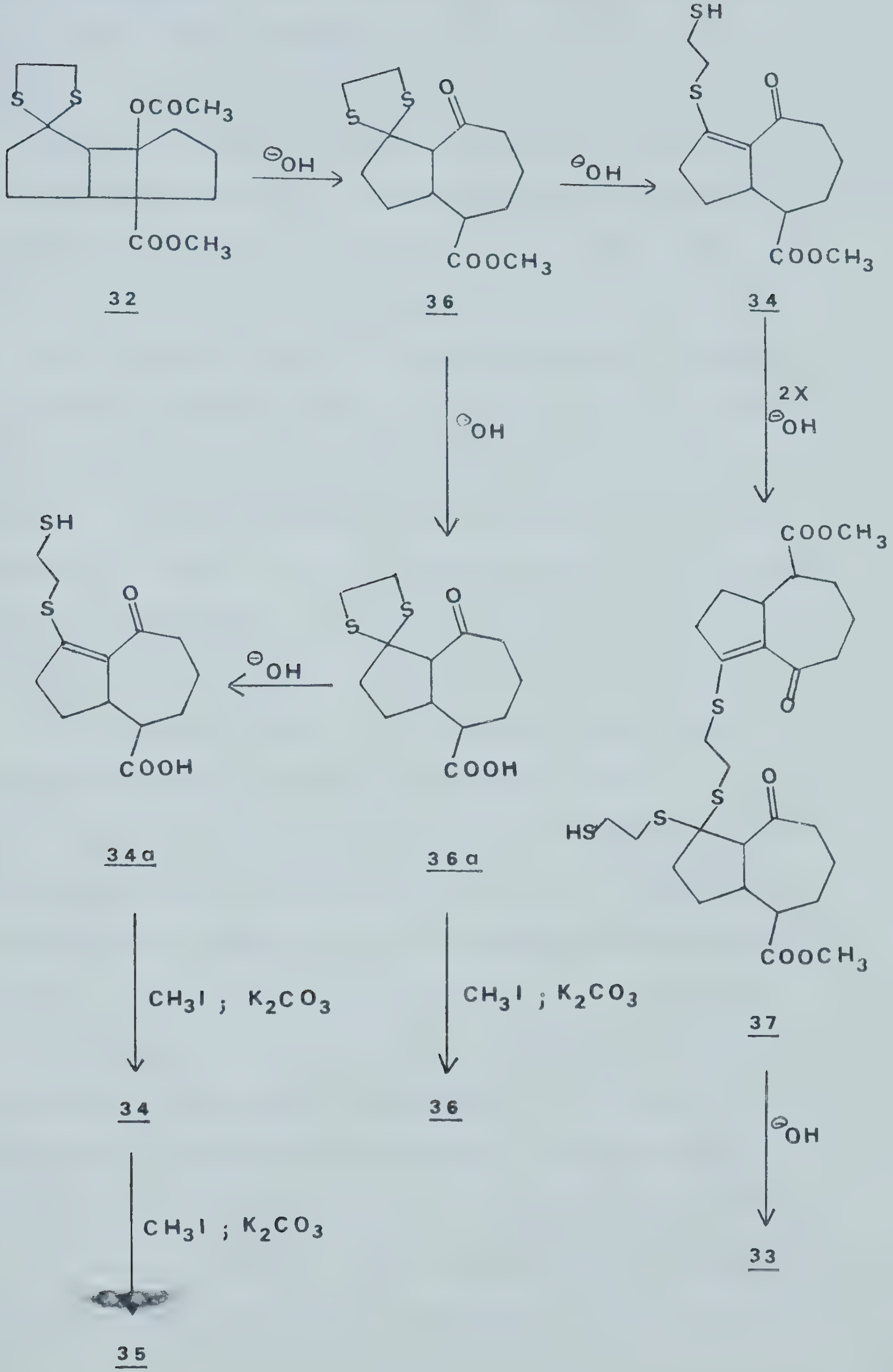


35



36

SCHEME III



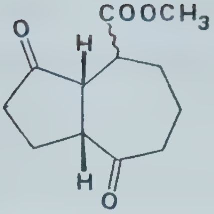
OCOCH3
COOCH3
32
⊖OH
O
COOCH3
36
⊖OH
SH
S
O
COOCH3
34
2X
⊖OH
⊖OH
SH
S
O
COOH
34a
⊖OH
O
COOH
36a
COOCH3
O
S
S
O
HS
S
COOCH3
37
CH3I ; K2CO3
34
CH3I ; K2CO3
36
CH3I ; K2CO3
35
⊖OH
33

a Michael addition path to yield 37 which in turn gave rise to the dimeric compound 33 by eliminating a molecule of 1,2-ethanedithiol. Hydrolysis of the mixture obtained from the thioketal formation reaction of the photoadducts with sodium hydroxide under the same conditions applied previously to 32, gave rise to a neutral mixture and an acidic material. The latter upon esterification (methyl iodide-potassium carbonate) gave a neutral mixture which was found to be identical with the one obtained directly from the hydrolysis reaction. The total yield of the mixture was 53% and no detectable amount of the compounds 33-36 was obtained. The mixture was shown to contain at least three compounds by its nmr spectrum exhibiting three methyl singlets at δ 3.57, 3.62 and 3.66 in 1:3:2 ratio. Upon treatment with mercuric chloride and mercuric oxide in aqueous methanol the mixture afforded as the only isolable products, cis and trans diones 24a and 24b which were found to be identical in all respects with authentic samples.[30] These findings unambiguously established the diastereomeric nature of these compounds as well as their gross structure as indicated in formula 38. Consequently, the precursor must be a diastereomeric mixture of 31a and 31b and the dethioketalization products that of 22a and 22b. The spectral data of 38 (in the mixture form) were also in agreement with the struc-

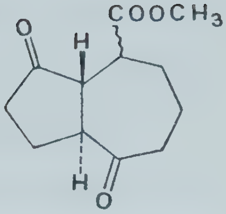
tural assignment. The nmr spectrum showed, in addition to the aforementioned ester methyl singlets, partially overlapped signals at δ 3.25 region for the four thioketal methylene protons. The ketone and the ester absorption bands appeared in the ir spectrum at 1700 and 1725 cm^{-1} respectively. The mass spectrum displayed a molecular ion peak at 300.0848 further supporting the assigned structure. The further structural evidence of 31a and 31b arose when their dethioketalization products 22a and 22b were subjected to hydrolysis with aqueous sodium hydroxide. After the esterification of the resulting acids with methyliodide and potassium carbonate, a mixture of cis and trans diones 24a and 24b were again obtained as the only isolable products.

In continuation of the present synthetic studies, ester 31 was converted directly into 38 by its treatment with sodium methoxide in refluxing methanol. The yield of 38 was comparable with that previously obtained by a two-step sequence but its preparation especially in large scale was found to be much simpler.

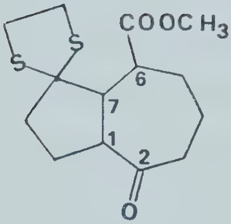
As noted before, zierone (1) has its C-10 methyl substituent separated from the highly sensitive dienone system and it is synthetically advantageous to insert this unit into the molecule at an early stage. With the structure of 38 now completely ascertained and its cyclopentanone moiety properly protected the subsequent studies



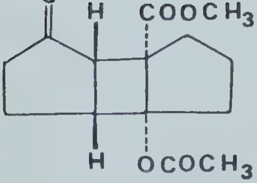
24a



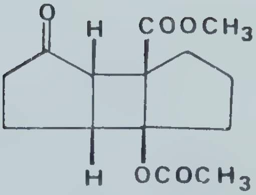
24b



38



22a



22b

were focused on the introduction of the necessary methyl group using its ketone carbonyl as a starting point.

Two different routes were investigated under the considerations that they would allow the control of the stereochemistry with respect to the C-10 methyl and C-1 hydrogen atom and thus lead to stereoselectively both the natural (cis) and the epi (trans) series of compounds. Wittig reaction of keto ester 38 with methylenetriphenylphosphorane (prepared in situ from methyltriphenylphosphonium bromide and methylsulfinyl carbanion) in dimethylsulfoxide[34] afforded a mixture of diastereomeric olefins 39a and 39b in 10% and 60% yield respectively. The structural assignments followed from their spectral data. The minor product which was faster moving on silica gel thin-layer chromatography showed in the ir spectrum absorption bands at 1725 and 1630 cm^{-1} for the ester and the double bonds respectively. Its nmr spectrum displayed a narrowly split doublet (<2 Hz) at δ 4.82 for the two olefinic protons, a methyl singlet at δ 3.68 and a multiplet centered at δ 3.23 for the four thioketal hydrogen atoms. In the case of the major isomer, these methylene protons appeared in the nmr spectrum as a singlet at δ 3.23 and additional signals were observed at δ 4.89 (vinylic), a "doublet" with a coupling constant of 8 Hz and at δ 3.65 (methyl), a singlet. In comparison with the corresponding absorp-

tion bands of 39a, both of its ester (1730 cm^{-1}) and double bond (1645 cm^{-1}) ir maxima appeared at slightly lower frequency. The nmr spectra coupled with their homogeneity in thin-layer chromatography strongly suggested both olefins 39a and 39b were single substances.* Whereas their structures were vigorously proven at this point, their stereochemistry could not be clearly defined and the tentative assignments of their partial stereochemistry was reached after further transformations and will be discussed in an appropriate later stage.

Not totally unexpectedly, catalytic hydrogenation of 39a and 39b caused some difficulties by virtue of the presence of sulfur atoms. This element is known to have noxious character toward catalyst. Attempted hydrogenation of 39a even by the use of the same amount (by weight) of 5% Pd/C, for example, gave rise to no traces of the desirable product but complete recovery of the starting material. This problem was circumvented by increasing the quantity of the catalyst used. A ten-fold excess by weight was found to be both "economical" and effective. Thus olefin 39a upon hydrogenation gave in a yield of 89% a single product whose

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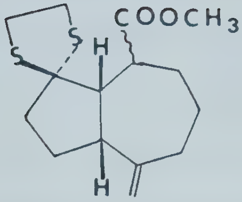
* It should be pointed out again that their precursor 38 was a mixture containing at least three stereoisomers. Under the Wittig reaction conditions, epimerization in particular at C-1 was, however, possible.

spectral data were in full agreement with structure 40. Two additional stereoisomers of 40 were obtained in a total yield of 69% when 39b was subjected to hydrogenation. Their ratio was approximately 5:4 based on the relative intensities of two ester singlets (δ 3.60 and 3.59), two thioketal singlets (δ 3.18 and 3.16) and two methyl doublets (δ 0.95 and 0.92).

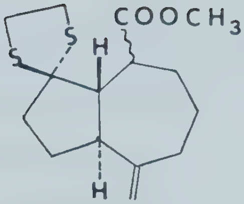
A fourth isomer of 40 was obtained from 38 by an alternative route. Treatment of 38 with methoxymethylenetriphenylphosphorane prepared *in situ* from methoxymethyltriphenylphosphonium chloride and methylsulfinylcarbanion[35] resulted in a 91% yield of two enol ethers of 41. The predominant isomer was obtained in pure form. Its ir spectrum displayed the ester absorption band at 1725 cm^{-1} and the double bond absorption band at 1665 cm^{-1}. In the nmr spectrum, a multiplet appeared at δ 5.85 for the vinylic proton. The two methyls both as singlets at δ 3.69 (enol ether) and 3.58 (ester) and a thioketal multiplet at δ 3.20 were also observed. On treatment with an ethereal solution saturated with perchloric acid at room temperature, enol ethers 41 were hydrolyzed smoothly to give a 96% yield of a mixture consisting of at least two diastereomers of aldehyde 42 as indicated by the nmr spectrum showing two doublets at δ 9.64 and 9.58 for the aldehydic proton and two methyl singlets at δ 3.68 and 3.67. The

major isomer isolated in pure form by crystallization from chloroform-ether showed, in addition to the ester absorption band at 1735 cm^{-1}, the characteristic aldehyde absorption bands at 2820, 2715 and 1720 cm^{-1} in the infrared spectrum. Its nmr spectrum displayed an aldehydic doublet at δ 9.62, a methyl singlet at δ 3.66 and a multiplet at δ 3.22 for the thioketal methylene protons. A molecular ion peak appearing in the mass spectrum at 314.10099 was consistent with the molecular formula of $C_{15}H_{22}O_3S_2$.

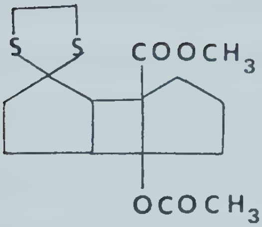
Attempted Wolff-Kishner reduction of aldehydes 42 was found to be complicated due to the instability of the thioketal group towards strong base, i.e., potassium hydroxide. Albeit in low yield (37%), the desirable conversion of the aldehyde group into a methyl was achieved by the use of Clemmensen reaction under the modified conditions.[36] Treatment of 42 (in the form of a diastereomeric mixture) with activated zinc powder and a solution of ether saturated with dry hydrogen chloride gave rise to a mixture of products; only one of them was found to possess the desired structure 40. The ir spectrum showed the absorption band for the ester carbonyl at 1720 cm^{-1} and the complete absence of those of the aldehyde group and the mass spectrum displayed a molecular ion peak at 300.12162 for a molecular composition of $C_{15}H_{24}O_2S_2$. In the nmr



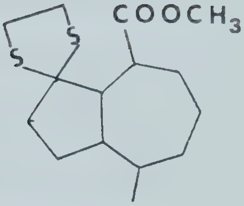
39a



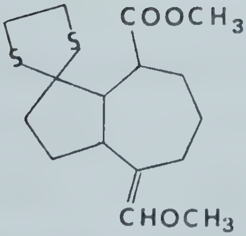
39b



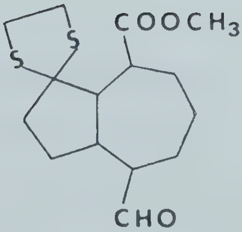
31



40



41



42

spectrum, the two methyls resonated at δ 3.65 and 0.95 as a singlet and a doublet respectively and the four thioketal protons appeared as a multiplet centered at δ 3.18. These spectral data were consistent with the structural assignment. Furthermore, a comparison of its spectral data with those of the three isomers of 40 obtained previously (*vide supra*), showed subtle but definite differences suggesting strongly their diastereomeric relationship.

Having four chiral centers in the molecule, a total of eight diastereomers of 40 are possible. In addition to the conformational non-rigidity of the seven-membered ring, the stereochemical assignments of the four isomers obtained are further complicated by the fact that the stability of hydroazulene systems in terms of the stereochemistry of the ring juncture is extremely sensitive to the substitution pattern and there is a lack of adequate models for comparison. Information presently available does not warrant concrete assignments to their stereochemistry and tentative ones were made on the basis of the following considerations.

To facilitate the discussion, the transformations of keto esters 38 to esters 40 are further summarized as follows. Reaction of 38 (consisting of at least three isomers) with methylenetriphenylphosphorane gave

two methylene derivatives; one of which (minor isomer) upon catalytic hydrogenation gave rise to a single isomer of 40 whereas the other afforded two additional isomers in approximately equal amounts under the same reduction conditions. On the other hand, Wittig reaction of 38 using methoxymethylenetriphenylphosphorane followed by the acid hydrolysis of the resulting methoxymethylene derivatives resulted in the formation of at least two aldehydes 42 whose reduction under modified Clemmensen reaction conditions gave rise to the fourth isomer of 40. With the presence of three assymmetric centers, 38 can possibly exist, with respect to the relative stereochemistry of C-6—C-7 and C-7—C-1*, in the following diastereomeric forms: cis(C-6—C-7)-trans(C-7—C-1), cis-cis, trans-cis, and trans-trans. The four theoretical stereoisomers can be further divided into two series with the C-6 carbomethoxyl group and C-7 hydrogen atom being either cis or trans. The fact that from three isomeric keto esters 38, only two methylene derivatives were produced strongly suggested that an epimerization process had taken place during the reaction and under rather mild conditions, of the three chiral centers, the one adjacent to the ketone carbonyl was most likely being involved. On this assump-

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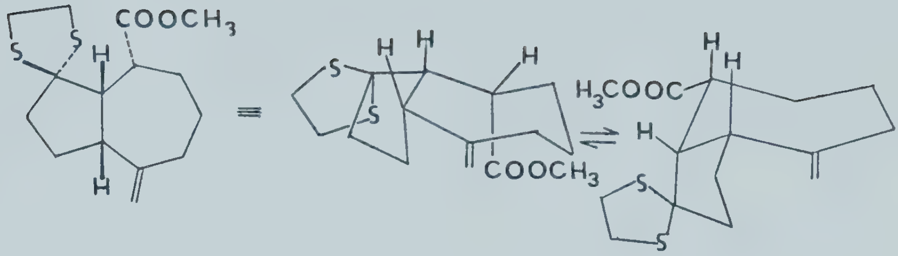
* For all the synthetic material, IUPAC numbering system is used.

tion, a cross-over between the two series is not permissible. As a result, two methylene derivatives must belong to each series possessing opposite relative stereochemistry at C-6 and C-7, i.e., one cis and the other trans. Furthermore, an examination of the Dreiding model reveals that, of the four possible diastereomers of the Wittig reaction product whose expectedly most stable conformations (maximum number of equatorial substituents and least amount of torsional and angular strains) are depicted as shown in stereoformulas 39c (trans-cis), 39d (trans-trans), 39e (cis-cis) and 39f (cis-trans), the two cis-fused compounds, 39c and 39e, have considerable steric discrepancy around their methylene group with the front side (cis to the ring juncture hydrogens) being much less hindered than the back. Hence, in each case the catalytic hydrogenation is expected to proceed in a highly stereoselective manner giving a predominant product, possibly to an exclusive extent. On the other hand, in the cases of the trans-fused compounds, 39d and 39f, both sides (top and bottom) of the double bond are shown to be more or less equally exposed. Their hydrogenation are thus expected to result in the formation of, in each case, a pair of epimers. Consequently, the isolation of a single compound from the hydrogenation of the minor Wittig reaction product requires its partial stereochemistry as shown in 39a and



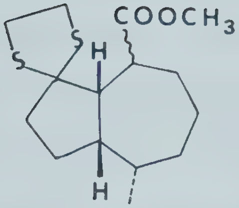
39c

39d

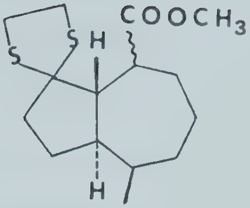
39e

39f

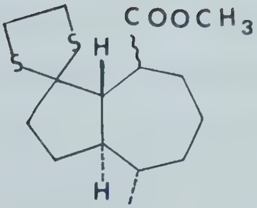
that of the hydrogenation product 40a as a result of the addition of the hydrogen molecule from its less hindered face. Similarly, the major isomer from the Wittig reaction must possess stereochemical formula of 39b and its hydrogenation products must be a pair of C-2 epimers 40b and 40c. Furthermore, 39a and 39b must have opposite stereochemistry at C-6 and the same applies to their hydrogenation products. The partial stereochemistry of the fourth isomer of 40 obtained from the second Wittig route could be tentatively assigned as shown in formula 40d on the following grounds. Its nmr spectrum was found to closely resemble that of 40a. For instance, both showed a multiplet for the thioketal grouping and the absence of any signals at δ 2.4-2.8 region. The remarkable similarity of their nmr spectra suggested an identical stereochemical arrangement of their ring junctures as a major change of the geometry of the molecule should result in a marked difference of the electronic environment of their protons and consequently, of their nmr signals. This was further evident from the fact that in the nmr spectrum of the two *trans*-fused compounds 40b and 40c the thioketal-methylenes appeared in both cases as a singlet and a two-proton multiplet was apparent at δ 2.75 region. Having the ring juncture of 40d assigned as *cis*, it remains to



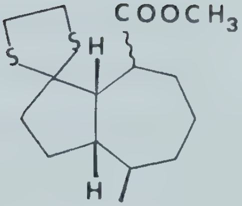
40a



40b



40c



40d

discuss its stereochemistry at C-2. It is noted that regardless of the relative stereochemistry of C-6 and C-7, of the two possible stereochemical arrangements with respect to the C-2 methyl and the C-1 hydrogen atom, the cis form is considered to be more stable. The difference in stability between the cis and the trans arrangements were disclosed by examining the Dreiding models. In spite of the fact that the molecules have no marked differences in their geometry by virtue of the identical ring fusions, the cis arrangement gains additional equatorial substituents on the cycloheptane ring. In case that C-6 and C-7 are cis, all four substituents (cyclopentane ring also being taken into account) can achieve an equatorial orientation in the cis form, whereas in the form of trans one of them must exist in an axial position. If C-6 and C-7 are trans, the cis form allows a total of three equatorial carbon-carbon bonds and the trans allows two. Furthermore, since prior to the generation of the methyl group, the chiral center of C-2 was epimerizable and since the reactions were carried under thermodynamically controlled conditions, it is logical to assign the resulting compound in the more stable form. It should be noted that two isomeric esters 39a and 39b were obtained from keto ester 38. The Wittig reaction of the latter with methoxymethylenetriphenyl-

phosphorane under similar conditions should also produce at least two isomers of ester 41 without regarding the possible geometric isomerism due to the newly introduced double bond. Subsequent transformations of 41 should then give rise to, besides 40d, at least another diastereomer. In fact both 41 and its hydrolysis product, aldehyde 42 were shown spectroscopically to contain at least two isomers. That the expected additional isomer of 40 was not detected could be due to that its direct precursor, i.e., one isomer of aldehyde 42, took a different course during the Clemmensen reduction reaction.

The above stereochemical assignments were made mainly on the basis of theoretical considerations. Experimentally, it leaves much to be desired. It should be noted that, though the stereochemistry of 40 is rather complex, only the relative stereochemical arrangement of C-1 and C-2 is of special significance with regard to the target molecule zierone (1). A possible approach to ascertain the relative stereochemistry of these two crucial centers of the four esters 40a-40d is to simplify their stereochemistry by introducing a double bond between their C-6 and C-7 carbons; thus making the stereochemical assignment a much easier task. Meanwhile, a molecule such as 43 is potentially useful as an intermediate toward the

total synthesis of zierone (1). Its conversion to 1 could be conceivably achieved in two steps as depicted in Scheme IV. Towards this end, 40a, a mixture of 40b and 40c, and 40d were hydrolyzed with mercuric chloride and mercuric oxide in aqueous methanol to give the corresponding keto esters 44a-44d. Subsequent incorporation of the desired double bond was attempted on 44d. Bromination with pyridinium bromide perbromide in glacial acetic acid followed by dehydrobromination of the resulting mixture of bromides, however, gave rise to mainly 45 and three other compounds 46, 47 and 48 in minor quantities but no traces of the desired product.*

As a consequence of the above findings, it was decided to confirm the stereochemistry of C-1 and C-2 in a later appropriate stage and to proceed with the synthesis in such a manner that the two remaining substituents and the needed functionalities would be incorporated sequentially. As the remaining carbon substituents are concerned, there are two alternatives by which the existing functionalities can be modified; either using compound 40 directly to first introduce the isopropylidene group or hydrolyzing the thioketal group in advance to facilitate the incorporation of a methyl

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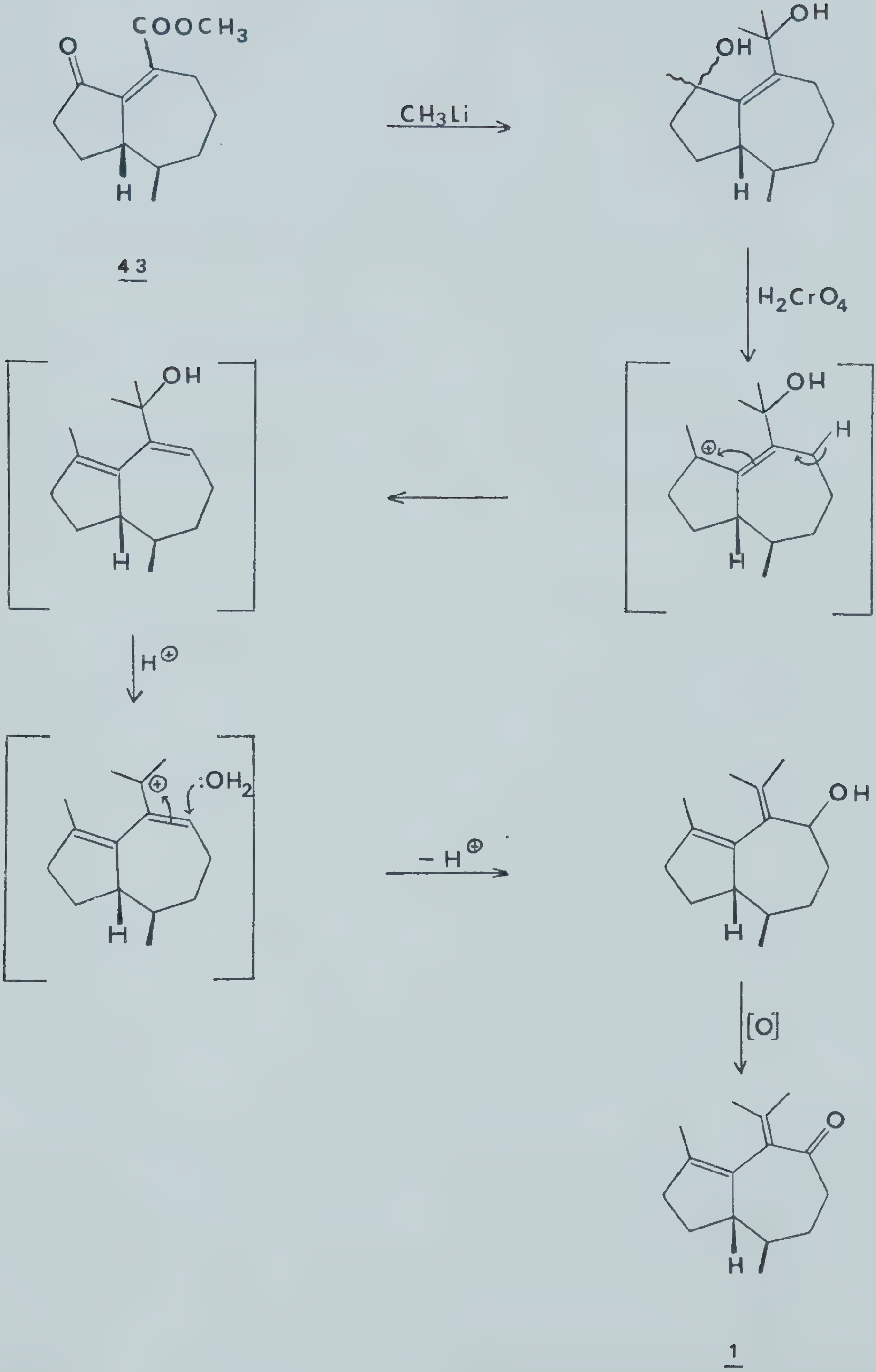
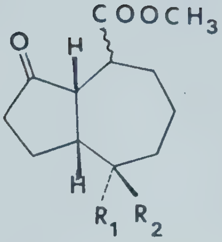
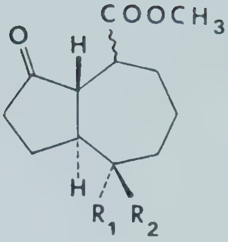
* Other methods for achieving this goal are presently being studied.

SCHEME IV





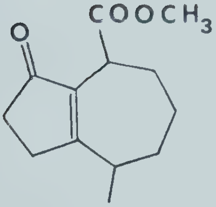


44a $R_1 = CH_3$; $R_2 = H$

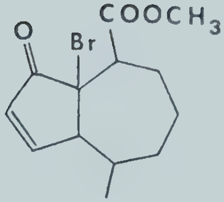
44b $R_1 = H$; $R_2 = CH_3$

44d $R_1 = H$; $R_2 = CH_3$

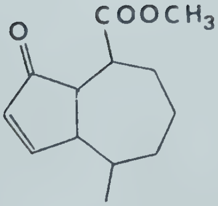
44c $R_1 = CH_3$; $R_2 = H$



45



46



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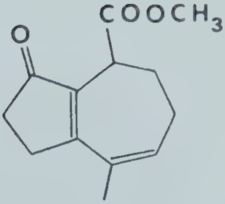


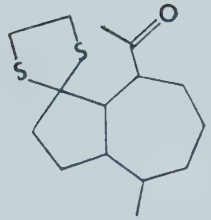
48

unit. The former route was followed. Upon treatment of 40 with methyllithium at room temperature for 3.5 hr, a 36% yield of 49 was obtained. An absorption band in the ir spectrum at 1705 cm^{-1} was indicative of the presence of a ketone carbonyl whereas the nmr spectrum showed a multiplet at δ 3.21 for the thioketal protons, two singlets at δ 2.24 and 2.10 for a total of three acetyl protons and a doublet at 0.94 with a coupling constant of 6 Hz for the methyl group. The molecular ion peak at 284.12677 further confirmed the assigned structure.

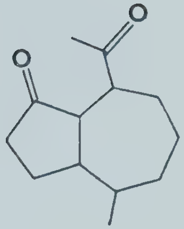
The thioketal protecting group was subsequently hydrolyzed by reacting 49 with mercuric chloride in aqueous acetonitrile. Purification of the resulting product by preparative tlc gave a 54% yield of 50 whose ir spectrum exhibited absorption bands at 1740 and 1710 cm^{-1} for the two ketone carbonyls. The nmr spectrum showed a singlet at δ 2.09 and a doublet at δ 0.98 for the two methyls. The mass spectrum displayed a mulecular ion peak at 208.1462 in agreement with the structure depicted.

An efficient construction of the parent ring skeleton of zierone (1) and its C-10 methyl substituent represents the current advance in our synthetic studies. Efforts are being made to further transform the properly located functionalities of the synthetic intermediates,

i.e. <u>40</u> and <u>50</u>, to the remaining dienone system of the target molecule in order to complete its synthesis.



49



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EXPERIMENTAL

General

Mass spectra were recorded on A.E.I. MS-50, MS-12, MS-9 and MS-2 mass spectrometers. Infrared (ir) spectra were obtained using a Perkin-Elmer Model 457 and 337 spectrophotometers. Nuclear magnetic resonance (nmr) spectra were recorded on Varian A-60, 90 MHz Perkin-Elmer 32 and HR-100 spectrometers. Unless otherwise stated, carbon tetrachloride was employed as the solvent and tetramethylsilane as internal standard. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Elemental analyses were performed by the microanalytical laboratory of this department. Gas chromatographic (glc) analyses were performed on an Aerograph A-90-P-3 with a column of 15% SE 30 on Chromosorb W.

Material

2-Cyclopenten-1-one was prepared from a mixture of 3,4- and 3,5-cyclopentenediol (Research Organic/Inorganic Chemical Corp.) according to the known procedure.[37] 2-Carbomethoxycyclopentanone was prepared by Dieckmann condensation of dimethyladipate[38] which was obtained from adipic acid according to the reported procedure.[39] Kieselgel was used as adsorbant for column chromatography.

1-Acetoxy-2-carbomethoxycyclopentene (23).

At 0°C, to a solution of 2-carbomethoxycyclopentanone (276.1 g, 2.04 mol) in pyridine (323.1 g, 4.09 mol) acetyl chloride (240.8 g, 3.07 mol) was added dropwise over a period of 1 hr. The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. After cooling to 0°C, ether (500 ml) was added and the resulting mixture was filtered. The filtrate was acidified with 10% sulfuric acid. The ether layer was separated and washed with saturated aqueous sodium chloride. The combined aqueous solution was extracted with chloroform (3 x 200 ml) and the chloroform solution was washed with saturated aqueous sodium chloride. The organic solutions were combined, dried over magnesium sulfate, filtered and distilled at 72-75°C/0.5 mm, giving 320.1 g (85% yield) of 1-acetoxy-2-carbomethoxycyclopentene (23): ir (neat) 1780 (enol acetate), 1725 (ester) and 1665 cm^{-1} (C=C); nmr δ 3.63 (s, 3H, $-COOCH_3$) and 2.30 (s, 3H, CH_3COO-).

7-Acetoxy-1-carbomethoxytricyclo[5.3.0.0^{2,6}]decan-3-one (22) and 1-Acetoxy-7-carbomethoxytricyclo[5.3.0.0^{2,6}]-decan-3-one (30).

The apparatus used for the photocycloaddition

is shown diagramatically in Fig. 1. 2-Cyclopenten-1-one (16.8 g, 0.21 mol) and 1-acetoxy-2-carbomethoxycyclopentene (23) (663.8 g, 3.60 mol) were placed in the reaction vessel. The solution was diluted with one liter of benzene and a constant and moderate flow of dry nitrogen was maintained to agitate the solution throughout the reaction period. Shortly after filling up the Dewar flask with crushed ice and H_2O, the solution was irradiated with a 450 W Hanovia high-pressure quartz mercury-vapor lamp using a pyrex filter for 24 hr during which time the progress of the reaction was monitored by gas chromatographic analysis of the aliquot of the reaction mixture. About 15% of the starting enone was left after the first irradiation and 14.07 g (0.17 mol) of 2-cyclopenten-1-one was added. The reaction mixture was again irradiated for 24 hr. The whole process was repeated five times more using the following amounts of the enone: 13.73 g (0.17 mol), 11.81 g (0.15 mol), 11.54 g (0.14 mol), 10.67 g (0.13 mol) and 10.11 g (0.12 mol). The solvent was removed under reduced pressure (aspirator) and the excess olefin (23) was recovered by distillation at 74°C/0.5 mm. The viscous oily residue was chromatographed using a solution of 2% ether in benzene to give a mixture of 22 and 30 (247.75 g, 86% yield): ir (neat) 1740 cm^{-1} (ketone

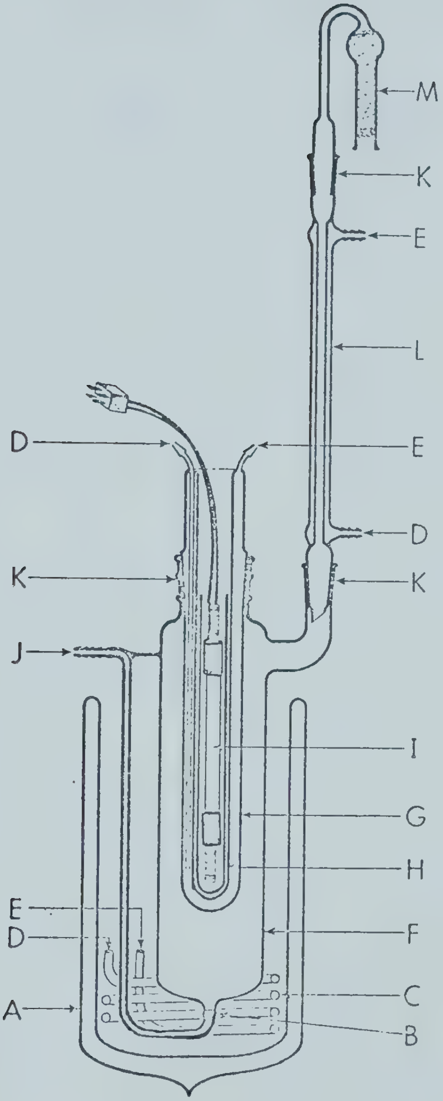

Fig. 1. A. Dewar flask; B. sintered glass filter; C. metal cooling coil; D. water inlet; E. water outlet; F. reaction vessel; G. quartz immersion well; H. pyrex filter; I. lamp; J. nitrogen gas inlet; K. ground glass joint; L. condenser; M. calcium chloride drying tube.

and esters); nmr δ 3.56 and 3.53 (both s, total 3H, $-COOCH_3$), 1.90 and 1.85 (both s, total 3H, CH_3COO-); mass spectrum M^+ 266.1151 (Calcd for $C_{14}H_{18}O_5$, 266.1154).

7-Acetoxy-1-carbomethoxy-3-ethylenedithiotricyclo-[5.3.0.0^{2,6}]decane (31) and 1-Acetoxy-7-carbomethoxy-3-ethylenedithiotricyclo[5.3.0.0^{2,6}]decane (32).

To a solution of 22 and 30 (11.7 g, 44.0 mmol) in 1,2-ethanedithiol (58 ml, 69 mmol) was added boron trifluoride etherate (5.8 ml). After stirring at room temperature for 4 hr (reaction monitored by tlc), the reaction mixture was poured into ice-cold 4N NaOH (50 ml) and extracted with chloroform (3 x 100 ml). The combined organic solution was washed with 100 ml each of 4N NaOH, water and saturated sodium chloride solution, dried ($MgSO_4$) and filtered. Concentration of the filtrate furnished a yellow oil which was purified by column chromatography. Elution with benzene gave 8.2 g (55% yield) of 31: m.p. 84-86°C (upon sublimation at 80-90°/0.1 mm); ir ($CHCl_3$) 1740 cm^{-1} (esters); nmr δ 3.60 (s, 3H, $-COOCH_3$), 3.20 (s, 4H, $-SCH_2CH_2S-$), 2.04 and 1.98 (both s, total 3H, CH_3COO-); mass spectrum M^+ 342.0959 (Calcd for $C_{16}H_{22}O_4S_2$, 342.0959).

Anal. Calcd for $C_{16}H_{22}O_4S_2$[32]: C, 56.12; H, 6.47;

S, 18.72. Found: C, 56.56; H, 6.40; S, 18.61.

Further elution with benzene gave 2.0 g (13% yield) of 32: m.p. 91-93°C (ether); ir ($CHCl_3$) 1740 cm^{-1} (esters); nmr δ 3.64 (s, 3H, $-COOCH_3$), 3.30 (s, 4H, $-SCH_2CH_2S-$) and 1.93 (s, 3H, CH_3COO-); mass spectrum: M^+ 342.0962 (Calcd for $C_{16}H_{22}O_4S_2{}^{32}$, 342.0959).

Anal. Calcd for $C_{16}H_{22}O_4S_2{}^{32}$: C, 56.12; H, 6.47; S, 18.72. Found: C, 56.14; H, 6.45; S, 18.18.

7-Acetoxy-1-carbomethoxytricyclo[5.3.0.0^{2,6}]decan-3-one (22a and 22b) and 1-Acetoxy-7-carbomethoxytricyclo-[5.3.0.0^{2,6}]decan-3-one (30).

To a solution of 31 (205 mg, 0.60 mmol) in methanol-H_2O (10:1; 38 ml) was added mercuric chloride (437 mg, 1.61 mmol) and mercuric oxide (349 mg, 1.61 mmol). After stirring for 24 hr at room temperature under a nitrogen atmosphere, the reaction mixture was refluxed for 1 hr. The mixture was filtered and the filtrate diluted with water. It was extracted with ether (3 x 40 ml), washed with ammonium acetate and saturated sodium chloride solution (50 ml each). Drying ($MgSO_4$), filtration and concentration gave an oily product which was purified by column chromatography using benzene as eluent to give 115 mg (72% yield) of 22a and 22b: ir ($CHCl_3$) 1740 cm^{-1} (esters

and ketone); nmr δ 3.60 and 3.59 (both s, total 3H, $-COOCH_3$), 1.99 and 1.94 (both s, total 3H, CH_3COO-); mass spectrum M^+ 266.1145 (Calcd for $C_{14}H_{18}O_5$, 266.1154). Under the same conditions, 32 (186 mg, 0.54 mmol) gave 55 mg (38% yield) of 30: ir ($CHCl_3$) 1740 cm^{-1} (ketone and esters); nmr δ 3.60 (s, 3H, $-COOCH_3$), 3.0 (d, 1H, J = 10 Hz, $-CO\overset{|}{C}H-$) and 1.98 (s, 3H, CH_3COO-); mass spectrum M^+ 266.1145 (Calcd for $C_{14}H_{18}O_5$, 266.1154).

Dimeric compound (33), 6-carbomethoxy-10-(1',4'-dithiabutyl)bicyclo[5.3.0]decen$^{\Delta 1,10}$-2-one (34), 6-carbomethoxy-10-(1',4'-dithiapentyl)bicyclo[5.3.0]-decen$^{\Delta 1,10}$-2-one (35) and 6-carbomethoxy-10-ethylene-dithiobicyclo[5.3.0]decan-2-one (36).

At 0°C, to a solution of ester 32 (277 mg, 0.81 mmol) in methanol (8 ml) 4N NaOH (4 ml) was added. The resulting solution, after stirring at room temperature under an atmosphere of nitrogen overnight, was diluted with water (20 ml) and extracted with chloroform (4 x 30 ml). The usual work-up of the extract gave 54 mg (23%) of 33: ir ($CHCl_3$) 1725 (ester) and 1640 cm^{-1} (enone); nmr δ 3.7 (s, 6H, 2X-$COOCH_3$), 3.3 (m, 2H, 2X-$\overset{|}{C}H-$) and 3.0 (s, 4H, $-SCH_2CH_2S-$); mass spectrum M^+ 506.1785 (Calcd for $C_{26}H_{34}O_6S_2$, 506.1797). The aqueous solution was acidified with 1N HCl and

extracted with chloroform (4 x 30 ml). The chloroform solution after washing with water, drying ($MgSO_4$), filtration and evaporation gave an acidic material (220 mg, 0.77 mmol) which was dissolved in acetone (20 ml). To this solution, potassium carbonate (300 mg, 2.2 mmol) was added and after stirring for 1 hr at room temperature under a nitrogen atmosphere, methyl iodide (2 ml, 32.1 mmol) was introduced. The resulting mixture after stirring for 16 hr was poured into water and extracted with chloroform (4 x 30 ml). The extract after work-up in the usual manner gave an oil which was subjected to column chromatography. Elution with benzene gave in order of increasing polarity the following compounds: keto-ester <u>36</u> [32 mg (14% yield from <u>32</u>)]: ir ($CHCl_3$) 1725 cm^{-1} and 1705 cm^{-1} (ester and ketone); nmr δ 3.60 (s, 3H, $-COOCH_3$) and 3.18 (s, 4H, $-SCH_2CH_2S-$); mass spectrum, M^+ 300; enone <u>35</u> (24 mg, 10% yield): ir ($CHCl_3$) 1725 (ester) and 1635 cm^{-1} (α,β-unsaturated ketone); nmr ($CDCl_3$) δ 3.70 (s, 3H, $-COOCH_3$) and 2.17 (s, 3H, $-SCH_3$); mass spectrum M^+ 314.1002 (Calcd for $C_{15}H_{22}O_3S_2^{32}$, 314.1011); enone <u>34</u> (45 mg, 20% yield): ir ($CHCl_3$) 1725 (ester) and 1635 cm^{-1} (α,β-unsaturated ketone); nmr ($CDCl_3$) δ 3.70 (s, 3H, $-COOCH_3$); mass spectrum M^+ 300.0863 (Calcd for $C_{14}H_{20}O_3S_2^{32}$, 300.0855).

6-Carbomethoxy-8-ethylenedithiobicyclo[5.3.0]decan-2-one (38).

Method A.

To a chilled solution (0°C) of 31 (7.4 g, 21.7 mmol) in methanol (60 ml) was added 4N NaOH (30 ml). After stirring at room temperature under a nitrogen atmosphere overnight the reaction mixture was poured into water and extracted with chloroform (4 x 50 ml). The combined organic layer was washed with water, dried ($MgSO_4$), filtered and concentrated. The crude product was crystallized from ether to give 2.0 g (30% yield) of 38. The aqueous layer was acidified with 2N HCl to pH 1 and extracted with chloroform (4 x 50 ml). The chloroform solution after the usual work-up gave 3.5 g (~56% yield) of the acidic product which without purification was dissolved in acetone (58 ml). To this solution, anhydrous potassium carbonate (3.5 g, 25.7 mmol) was added. The reaction mixture was stirred at room temperature for 1 hr under a nitrogen atmosphere and methyl iodide (3.2 ml, 51.4 mmol) was introduced. Stirring was continued for 16 hr and the resulting mixture was worked-up in the usual manner to give an oil which was subjected to column chromatography using benzene as eluent. The material thus obtained was crystallized from ether to give additional 1.3 g of 38 (total 53% yield from 31). The crystalline

keto ester 38, m.p. 88-90°C showed the following spectral data: ir ($CHCl_3$) 1725 (ester) and 1700 cm^{-1} (ketone); nmr δ 3.66, 3.62 and 3.57 (all s, total 3H, $-COOCH_3$), 3.25 (s, 4H, $-SCH_2CH_2S-$); mass spectrum M^+ 300.0848 (Calcd for $C_{14}H_{20}O_3S_2{}^{32}$, 300.0855).

Anal. Calcd for $C_{14}H_{20}O_3S_2$: C, 55.97; H, 6.71; S, 21.35. Found: C, 56.22; H, 6.77; S, 21.38.

Method B.

To a solution of sodium methoxide in methanol (prepared by addition of 420 mg (18.3 g - atom) of sodium to 90 ml of methanol), was added dropwise a solution of ester 31 (1.56 g, 4.56 mmol) in 10 ml. of methanol. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 48 hr. Methanol was partially removed under reduced pressure and the residue was dissolved in chloroform, washed with H_2O, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the resulting oil using a solution of 3% ether in benzene as eluent gave 719 mg of 38 (53% yield).

6-Carbomethoxybicyclo[5.3.0]deca-2,8-dione (24a and 24b).

A. From 22:

Keto ester 22 (143 mg, 0.54 mmol) was dissolved in methanol (4 ml) and 4N NaOH (2 ml) was added. After refluxing for 16 hr, the reaction mixture was

cooled to 0°C, diluted with water, washed twice with chloroform and acidified with 1N HCl. Extraction with chloroform followed by the usual work-up of the extracts gave an acidic material (23 mg, 0.11 mmol) which without purification was dissolved in acetone and anhydrous potassium carbonate (30 mg, 0.22 mmol) was added. The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 1 hr and methyl iodide (0.2 ml, 3.2 mmol) was introduced. The stirring was continued for 16 hr and the resulting mixture was worked up in the usual manner to give an oil which was purified by column chromatography. The purified products 24a and 24b (8.6 mg, 36% yield) were found to be identical with the authentic samples.[30]

B. From 38:

To a solution of 38 (50 mg, 0.17 mmol) in methanol-H_2O (10:1; 11 ml) was added mercuric chloride (110 mg, 0.41 mmol) and mercuric oxide (90 mg, 0.41 mmol). The reaction mixture was stirred at room temperature for 23 hr under a nitrogen atmosphere. The mixture was filtered and the filtrate was diluted with water and extracted with methylene chloride (3 x 40 ml). The organic layer was washed with sat'd. ammonium acetate and water (30 ml each), dried ($MgSO_4$), evaporated and purified by preparative tlc [silica gel; ether-benzene (1:3) elution] to give

a mixture of 24a and 24b (32 mg, 84% yield).

6-Carbomethoxy-8-ethylenedithio-2-methylenebicyclo-[5.3.0]decane (39a) and (39b).

A 2M stock solution of methylsulfinyl carbanion[40] in dimethylsulfoxide was prepared as follows: sodium hydride (2.4 g, 0.1 mol) was placed in a nitrogen-flushed three-necked flask and washed thrice with skelly B. After traces of skelly B was removed *in vacuo*, freshly distilled dimethylsulfoxide was added and the mixture was heated at 70-75° for 40 min or until the evolution of hydrogen had ceased. Heating was continued for an additional 10 min at 75-80°C.

To a solution of methyltriphenylphosphonium bromide (1.9 g, 5.3 mmol) in dimethylsulfoxide (11 ml), the above stock solution of methylsulfinyl carbanion in dimethylsulfoxide (2.7 ml, 5.4 mmol) was added. After it was stirred at room temperature for 10 min under a nitrogen atmosphere, a solution of keto ester 38 (321 mg, 1.1 mmol) in dimethylsulfoxide (8 ml) was added in one portion. The reaction mixture was heated at 40°C for 6 hr and poured into ice-cold water (2 ml). Extraction with methylenechloride (4 x 30 ml) followed by the usual work-up of the extracts gave an oily product which was purified by preparative tlc [silica gel; ether-skelly B (1:4) elution] to give 39a (31 mg,

10% yield) and 39b (192 mg, 60% yield). These compounds showed the following spectral data: 39a: ir ($CHCl_3$) 1725 (ester) and 1630 cm^{-1} (C=C); nmr δ 4.82 (d, 2H, J = <2 Hz, $=CH_2$), 3.68 (s, 3H, $-COOCH_3$), 3.23 (s, 4H, $-SCH_2CH_2S-$); 39b: ir ($CHCl_3$) 1730 cm^{-1} (ester) and 1645 cm^{-1} (C=C); nmr δ 4.89 (d, 2H, J = 8 Hz, $=CH_2$), 3.65 (s, 3H, $-COOCH_3$), 3.23 (s, 4H, $-SCH_2CH_2S-$).

6-Carbomethoxy-8-ethylenedithio-2-methylbicyclo[5.3.0]-decane (40a).

Ester 39a (19 mg, 0.065 mmol) was dissolved in ethyl acetate (10 ml) and 5% Pd/C (193 mg) was added. The resulting mixture was stirred under an atmosphere of hydrogen overnight. The catalyst was filtered and the filtrate concentrated. Column chromatography of the residue using benzene as eluent gave 40a (17.2 mg, 89% yield): ir ($CHCl_3$) 1720 cm^{-1} (ester); nmr δ 3.52 (s, 3H, $-COOCH_3$), 3.05 (m, 4H, $-SCH_2CH_2S-$) and 0.98 (d, 3H, J = 6 Hz, $-CH_3$); mass spectrum M^+ 300.1226 (Calcd for $C_{15}H_{24}O_2S_2^{32}$, 300.1218).

6-Carbomethoxy-8-ethylenedithio-2-methylbicyclo[5.3.0]-decane (40b and 40c).

Hydrogenation of 39b (126.3 mg, 0.42 mmol) under the same conditions as above gave 40b and 40c (88.2 mg,

69% yield): ir ($CHCl_3$) 1725 cm^{-1} (ester); nmr δ 3.60, 3.59 (both s, total 3H, $-COOCH_3$), 3.18, 3.16 (both s, total 4H, $-SCH_2CH_2S-$) and 0.95 and 0.92 (2 d, 3H, J = J' = 6 Hz, $-CH_3$); mass spectrum, M^+ 300.1237 (Calcd for $C_{15}H_{24}O_2S_2{}^{32}$, 300.1218).

6-Carbomethoxy-8-ethylenedithio-2-methoxymethylene-bicyclo[5.3.0]decane (41).

To a stirred suspension of methoxymethyltriphenylphosphonium chloride[41] (3.05 g, 8.88 mmol) in dimethylsulfoxide (170 ml) was added 2M methylsulfinylcarbanion stock solution (4.45 ml). The deep red mixture was stirred at room temperature for 10 min and a solution of keto ester 38 (534 mg, 1.78 mmol) in dimethylsulfoxide (17 ml) was added. The reaction mixture after stirring at room temperature for 16 hr was poured into ice water and extracted with ether (3 x 200 ml). The combined ether solution was washed with water, dried ($MgSO_4$), filtered and evaporated to dryness to give an oil which on column chromatography using 60% ether in pentane as eluent yielded 41 (534 mg, 91% yield): ir (neat) 1725 (ester) and 1665 cm^{-1} (C=C); nmr δ 5.85 (m, 1H, vinylic proton) 3.69 (s, 3H, enol ether), 3.58 (s, 3H, $-COOCH_3$) and 3.20 (s, 4H, $-SCH_2CH_2S-$).

6-Carbomethoxy-8-ethylenedithiobicyclo[5.3.0]decane-2-aldehyde (42).

Compound 41 (534 mg, 1.63 mmol) was dissolved in an ethereal solution saturated with perchloric acid. After stirring at room temperature for 16 hr, the reaction mixture was diluted with water and extracted with chloroform (3 x 125 ml). The usual work-up of the chloroform solution followed by column chromatography of the resulting oily product using a solution of 3% ether in benzene as eluent gave 42 (490 mg, 96% yield from 41): m.p. 83-84° ($CHCl_3$-ether); ir ($CHCl_3$) 2820, 2715 and 1720 cm^{-1} (aldehyde) and 1735 cm^{-1} (ester); nmr ($CDCl_3$) δ 9.67 and 9.58 (2 d, 1H, J = J' = 3 Hz, -CHO), 3.68 & 3.67 (2 s, 3H, $-COOCH_3$) and 3.22 (s, 4H, $-SCH_2CH_2S-$); mass spectrum M^+ 314.10099 (Calcd for $C_{15}H_{22}O_3S_2{}^{32}$, 314.10104).

Anal. Calcd for $C_{15}H_{22}O_3S_2{}^{32}$: C, 57.29; H, 7.06; S, 20.39. Found: C, 56.97; H, 6.98; S, 19.97.

6-Carbomethoxy-8-ethylenedithio-2-methylbicyclo[5.3.0]-decane (40d).

At 0°C, aldehyde 42 (250 mg, 0.80 mmol) was dissolved in a solution of ether (125 ml) saturated with dry hydrogen chloride and activated zinc powder[36] (12 gm, 0.19 mol; prepared by stirring zinc dust in

1N HCl for 15 min, washed with water, ethanol, dry acetone and dry ether, and heated at 90°C under reduced pressure for 10 min) was added slowly in portions over a 20 min period. After stirring for an additional 15 min the reaction mixture was filtered and the filtrate was poured into ice water and extracted with ether (3 x 100 ml). The ether solution was washed with water, dried ($MgSO_4$), filtered and concentrated. Preparative tlc of the crude product using a solution of 35% ether in petroleum ether as eluent gave 40d (89 mg, 37% yield): m.p. 84-86°C (ether): ir ($CHCl_3$) 1720 cm^{-1} (ester); nmr ($CDCl_3$) δ 3.65 (s, 3H, $-COOCH_3$), 3.18 (m, 4H, $-SCH_2CH_2S-$) and 0.95 (d, 3H, J = 6 Hz, $-CH_3$); mass spectrum M^+ 300.12162 (Calcd for $C_{15}H_{24}O_2S_2{}^{32}$, 300.12198).

6-Carbomethoxy-2-methylbicyclo[5.3.0]decan-2-one (44a).

To a solution of 40a (41.6 mg, 0.14 mmol) in methanol-H_2O (10:1; 7.8 ml), was added mercuric chloride (88.8 mg, 0.33 mmol) and mercuric oxide (70.9 mg, 0.33 mmol). The resulting mixture was stirred overnight, filtered, diluted with water and extracted with ether (3 x 20 ml). The combined ether solution was washed with ammonium acetate and saturated aqueous sodium chloride, dried ($MgSO_4$) and concentrated to give an oil which was purified by column chromatography.

Elution with benzene gave 44a (11.3 mg, 36% yield): ir ($CHCl_3$) 1730 cm^{-1} (ketone and ester); nmr δ 3.58 (s, 3H, $-COOCH_3$) and 0.92 (d, 3H, J = 6 Hz, $-CH_3$); mass spectrum M^+ 224.14107 (Calcd for $C_{13}H_{20}O_3$, 224.14124).

6-Carbomethoxy-2-methylbicyclo[5.3.0]decan-2-one (44b and 44c).

The mixture (40b and 40c) (132 mg, 0.44 mmol) was treated with mercuric chloride (282.5 mg, 1.05 mmol) and mercuric oxide (225.5, 1.05 mmol) in the same manner as above to give 44b and 44c (69.4 mg, 70% yield) which showed the following spectral data: ir ($CHCl_3$) 1725 cm^{-1} (ketone and ester); nmr δ 3.65 (s, 3H, $-COOCH_3$) and 0.99 (d, 3H, J = 6 Hz, $-CH_3$); mass spectrum M^+ 224.14086 (Calcd for $C_{13}H_{20}O_3$, 224.14124).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.40; H, 8.99.

6-Carbomethoxy-2-methylbicyclo[5.3.0]decan-2-one (44d).

To a solution of 40d (398 mg, 1.33 mmol) in methanol-H_2O (10:1; 120 ml) was added mercuric chloride (1.13 gm, 4.20 mmol) and mercuric oxide (900 mg, 4.20 mmol). The resulting mixture was stirred for 3 hr, filtered and diluted with water. Extraction with

chloroform followed by the work-up of the chloroform solution in the usual manner gave an oil which was purified by preparative tlc [silica gel; ether-pentane (1:1) elution]. Compound 44d (68 mg, 23% yield) thus obtained showed the following spectral data: ir (neat) 1730 cm^{-1} (ketone and ester); nmr δ 3.61 (s, 3H, $-COOCH_3$) and 1.00 (d, 3H, J = 6 Hz, $-CH_3$); mass spectrum: M^+ 224.14107 (calcd for $C_{13}H_{20}O_3$, 224.14124).

6-Carbomethoxy-2-methylbicyclo[5.3.0]decen$^{\Delta1,7}$-8-one (45), 7-bromo-6-carbomethoxy-2-methylbicyclo[5.3.0]-decen$^{\Delta9,10}$-8-one (46), 6-carbomethoxy-2-methylbicyclo-[5.3.0]decen$^{\Delta9,10}$-8-one (47) and 6-carbomethoxy-2-methylbicyclo[5.3.0]deca-2,7-diene-8-one (48).

To a solution of keto ester 44d (68 mg, 0.3 mmol) in glacial acetic acid (7 ml), was added pyridinium hydrobromide perbromide (135 mg, 1.2 eq) and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1.5 hr or until the evolution of hydrogen bromide gas had ceased. The mixture was extracted with chloroform and the organic layer was washed with saturated solution of sodium bicarbonate and 1N hydrochloric acid, dried ($MgSO_4$) and evaporated. The crude product was refluxed with pyridine (7 ml) for 15 hr, extracted with chloroform,

washed the organic portion with 1N hydrochloric acid and after the usual work-up followed by purification by column chromatography using benzene as eluent, gave four products: bromoenone 46 (10 mg, 11% yield): ir (neat) 1730 (ester and ketone) and 1640 $\mathrm{cm^{-1}}$ (C=C); nmr δ 7.78 (d, 1H, J = 1 Hz, $=\overset{\mathrm{H}}{\mathrm{C}}\text{-CO-}$), 6.74 (m, 1H, vinyl proton), 3.60 (s, 3H, $-\mathrm{COOCH_3}$) and 1.30 (d, 3H, J = 2 Hz, $-\mathrm{CH_3}$); mass spectrum $\mathrm{M^+}$ = 302; enone 47 (7 mg, 11% yield): ir (neat) 1730 (ester) 1705 (enone) and 1640 $\mathrm{cm^{-1}}$ (C=C); nmr δ 7.69 (m, 1H, $=\overset{\mathrm{H}}{\mathrm{C}}\text{-CO-}$), 6.21 (m, 1H, vinyl proton), 3.60 (s, 3H, $-\mathrm{COOCH_3}$), 1.12 (d, 3H, J = 6 Hz, $-\mathrm{CH_3}$); mass spectrum $\mathrm{M^+}$ 222; enone 45 (17 mg, 26%): ir (neat) 1730 $\mathrm{cm^{-1}}$ (ester), 1690 (enone) and 1640 (C=C); nmr δ 3.65 and 3.64 (both s, total 3H, $-\mathrm{COOCH_3}$), 1.24 and 1.18 (both d, total 3H, J = J' = 2 Hz, $-\mathrm{CH_3}$); mass spectrum $\mathrm{M^+}$ 222; dienone 48 (5 mg, 8% yield); ir (neat) 1730 (ester), 1690 (enone) and 1600 $\mathrm{cm^{-1}}$ (diene); nmr δ 6.17 (m, 1H, vinyl proton), 3.63 (s, 3H, $-\mathrm{COOCH_3}$) and 1.28 (s, 3H, $-\mathrm{CH_3}$); mass spectrum $\mathrm{M^+}$ 220.

6-Acetyl-8-ethylenedithio-2-methylbicyclo[5.3.0]decane (49).

To a solution of 40 (244 mg, 0.81 mmol) in anhydrous ether (10 ml), was added methyllithium (2.06M, 2 ml, 4.12 mmol). The reaction mixture after stirring

at room temperature for 3.5 hr was cooled to 0°C and 0.5N HCl (10 ml) was added. Extraction with chloroform (4 x 25 ml) followed by the usual work-up of the extracts gave an oil which was subjected to preparative tlc [silica gel; ether-pentane (1:2) elution] to give 83 mg (36% yield) of 49: ir ($CHCl_3$) 1705 cm^{-1} (ketone); nmr ($CDCl_3$) δ 3.21 (s, 4H, $-SCH_2CH_2S-$), 2.24, 2.10 (both s, total 3H, $-COCH_3$) and 0.94 (d, 3H, J = 6 Hz, $-CH_3$); mass spectrum M^+ 284.12677 (Calcd for $C_{15}H_{24}OS_2{}^{32}$, 284.12687).

6-Acetyl-2-methylbicyclo[5.3.0]decan-8-one (50).

Ketone 49 (140 mg, 0.49 mmol) was dissolved in CH_3CN-H_2O (3:1; 8 ml) and mercuric chloride (420 mg, 1.5 mmol) was added. The reaction mixture was stirred at room temperature for 20 hr. The resulting mixture was filtered and the filtrate was diluted with water and extracted with chloroform. The chloroform solution was washed with saturated ammonium acetate, dried over magnesium sulfate, filtered and concentrated. Preparative tlc (silica gel) of the crude product with ether-pentane (1:1) elution gave 55 mg (54% yield) of 50: ir ($CHCl_3$) 1740 (five-membered ring ketone) and 1710 cm^{-1} (ketone); nmr ($CDCl_3$) δ 2.09 (s, 3H, $-COCH_3$) and 0.98 (3H, d, J = 6 Hz, $-CH_3$); mass spectrum M^+ 208.1462 (Calcd for $C_{13}H_{20}O_2$, 208.1463).

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